Treating depressive symptoms at their roots

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A wide range of compounds is on the market to ameliorate depressive symptoms. However, their efficiency is achieved only after long periods of treatment and not in all patients. Inserm researchers identified early cellular changes in the brain for the emergence of depressive symptoms, and a novel promising drug target. These results were published in the journal *Nature Medicine* on Janaury 25th, 2016.

The aim of researchers Manuel Mameli and Dr. Salvatore Lecca was to understand the initial cellular modifications occurring after a stressful aversive experience. Protracted stress and aversive experiences are, indeed, a trigger that engages depressive behaviors in animals and humans.

Using electrophysiological, viral-based and pharmacological approaches, researchers found that the activity of neurons located in the lateral habenula—a cerebral nucleus for aversion and disappointment—increased following a stressful experience due to the reduced function of two proteins controlling neuronal function (GABAB and GIRK).

Inserm scientists designed a rescue strategy that reversed the cellular modifications and ameliorated depressive symptoms after aversive experience by targeting a specific phosphatase (PP2A). By employing a rodent model of mood disorders (learned helplessness), that recapitulates a number of behavioral phenotypes typical of human depression, they have shown that the inhibition of PP2A rapidly ameliorated the behavioral phenotype of mice.

"Our study unravels unknown early cellular mechanisms able to trigger complex behavioral responses. Our study further highlights the role of the lateral habenula in the aetiology of depression. Our results provide insights on a novel potential pharmacological target that could be studied for a therapy of mood disorders," says Mameli.

More information: Rescue of GABAB and GIRK function in the lateral habenula by protein phosphatase 2A inhibition ameliorates depression-like phenotypes in mice, *Nature Medicine*, DOI: 10.1038/nm.4037

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